CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-237

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-237

DRUG PRODUCT: Sotalol Hydrochloride

FIRM: Genpharm

DOSAGE FORM: Tablets

STRENGTHS: 80, 120, 160 & 240 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form:

The dosage form will be manufactured, controlled and processed, packaged and labeled at

GENPHARM, INC.
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6

EER Attached, Acceptable. November 18, 1998.

Manufacturer-Active Ingredients:

The drug substance, Sotalol Hydrochloride is manufactured by:

The drug substance is manufactured per
A LOA to reference this DMF is included. The letter is from
1
is the U.S.Agent for

M.P. Selvam, reviewed the on April 14, 1999, found Adequate and thereafter there is no update.

Contract Laboratories:

No contract firms are listed in regard to the manufacture or testing of the drug substance or finished drug product.

BIO STUDY:

The new amendment (8-23-1999)reviewed by L.W. Chuang and the approval letter sent on 8-30-1999 for 80,120, 160 and 240 mg tablets.

The Bio review recommended the Firm that the dissolution testing should be conducted in 900 mL of water, at 37 C using USP Apparatus II at 50 rpm. And the test product should meet the following specifications recommended by the Agency.

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The Waiver has been granted for in vivo bio-equivalence testing on its 80 mg 120, and 160 mg products per 21 CFR section 320.22(d)(2).

Dissolution:	NLT of label claim is dissoluted in 30 minutes
Assay:	95.0 - 105.0%

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Both drug substance and drug product are not USP. Revised MV Package with the recent specifications submitted to the Philadelphia District Laboratory and it is pending.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Lots used in Stability study:

80 mg tablet:	Lot # 104818;	tablets
120 mg tablet:	Lot # AA52;	tablets
160 mg tablet:	Lot # 104819;	tablets
240 mg tablet:	Lot # 104820;	tablets.

3 month accelerated (40°C/75% RH) are included for the 80 mg, 120 mg, 160 mg and 240 mg tablets packaged in the proposed market containers. Room temperature testing will be performed at 25°C ± 2°C and 60%±5% RH.

3 months room temperature data was included for the 80 mg, 120 mg, 160 mg and 240 mg tablets packaged in the bulk container to support the proposed 3 month expiration date for the product in bulk containers.

Dissolution: **The Bio review recommended the Firm that the dissolution testing should be conducted in 900 mL of water, at 37 C using USP Apparatus II at 50 rpm.**

NLT of label claim is dissolved in 30 minutes
Assay: 95.0 - 105.0%

Impurities:

Impurity I:
Impurity II:
Impurity III:
Largest Single Unknown:
Total Impurities:

LABELING:

The name, structure, molecular formula and molecular weight are as the same as the Innovator's.

The inactive ingredients' list appears to be Satisfactory.

The HOW SUPPLIED section appears to be Satisfactory

Final Amendment Reviewed by Adolph Vezza, 9/15/1999

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Satisfactory

The DMF for the Drug substance Sotalol HCl was reviewed by on 4-14-1999 and found to be adequate. Thereafter there is no update in the DMF.

Completed batch records were included for the following test batches of finished drug product:

80 mg tablet: Lot # 104818; tablets
120 mg tablet: Lot # AA52; tablets
160 mg tablet: Lot # 104819; blets
240 mg tablet: Lot # 104820, tablets.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

80 mg tablet:	Lot # 104818;	tablets
120 mg tablet:	Lot # AA52;	tablets
160 mg tablet:	Lot # 104819;	tablets
240 mg tablet:	Lot # 104820;	tablets.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The manufacturing process used for the test batches were the same as the manufacturing process described in the blank batch records. The manufacturing instructions were clearly written and the formulations appeared to be correct.

A commitment to perform process validation studies on the first three post approval production lots is included p. 3049.
The instructions are clearly written and the formulation is correct and meets OGD requirement.

CHEMIST: Mouna P. Selvam, Ph.D., **DATE:** 10/12/1999

SUPERVISOR: Ubrani V. Venkatartam, Ph.D., **DATE:** 10/12/1999

U. V. Venkatartam
10/13/99.

Telephone Conversation Memorandum

ANDA: 75-237

DRUG: Sotalol Hydrochloride Tablets, 80 mg,

FIRM: Genpharm Inc.

PERSONS INVOLVED: Tirsa Uphal, Genpharm
Tim Ames, FDA

PHONE NUMBER: 416-207-1216 x223

DATE: October 7, 1999

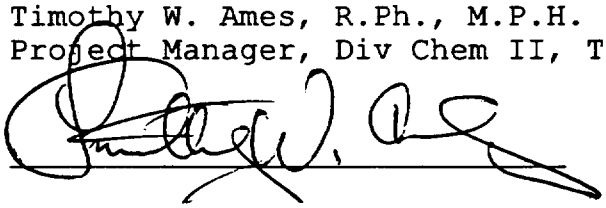
Called firm to relate Vsayeed's requests:

Firm's spec for Blister Leak Test of is unacceptable. Firm should revise to just as per previous requests.

Firm should also include a test for chloride (an ID test performed by the drug substance manufacturer) in the drug substance testing and include on their COA.

Ms Uphal agreed to amend their application with these requests as a telephone amendment.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD



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File:

(this supersedes the tentative approval summary dated 12-4-98)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-237** Date of Submission: **September 9, 1999**

Applicant's Name: **GENPHARM INC.**

Established Name: **Sotalol HCl Tablets, 80 mg, 120 mg, 160 mg, 240 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 1000s - 80 mg, 120 mg, 160 mg, 240 mg
Satisfactory in final print as the 10/14/98 submission.

Unit Dose Blister Label: 120 mg and 240 mg
Satisfactory in final print as the 10/14/98 submission.

Unit Dose Carton Label: 100s (10 x 10) - 120 mg and 240 mg
Satisfactory in final print as the 10/14/98 submission.

Professional Package Insert Labeling:
Satisfactory in final print as the 9/9/99 submission.

Revisions needed post-approval:

May Relocate Rx Only.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Betapace®

NDA Number: 19-865

NDA Drug Name: Betapace® (Sotalol Hydrochloride) Tablets

NDA Firm: Berlex Laboratories, Inc.

Date of Approval of NDA Insert and supplement #: 8/23/99 (S-008)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-sides of Betapace.

Basis of Approval for the Carton Labeling: Side-by-sides of Betapace.

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? SEE NOTE TO THE CHEMIST Must the package insert accompany the product? YES - FOR THE UNIT DOSE	*		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? COMMENT MADE		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? NOT USP If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? YES	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: (comments from previous review)

1. I was unable to find a components and composition statement for the 120 mg strength. Do you know if the firm submitted one?

2. The following are questions from the previous review/reviewer. Please discard if you have already answered these questions in the A/blue volume labeling review. I did my review with the B/red volumes.

   a. Are all the container lids screw caps? Per chemistry review No. 1, no CRCs have been proposed but they have been put on stability.

   b. Is this drug product light-sensitive? Per consult with chemist D. Shostak - unable to find any information on this but because of the fact that the innovator's storage statement says "Dispense in a well-closed container." (This ANDA has "Dispense in a tight, light-resistant container.") it is fair to assume that the drug product is stable in light. ANDA containers are of HDPE - impervious to light.

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling of Betapace® (Berlex - approved 8/23/99 & revised 12/98). NDA 19-865/S-008

2. The RLD has orphan drug exclusivity until October 30, 1999. GenPharm has stated that they will not market this drug product before then.

3. Packaging:

RLD -80 mg, 160 mg, 240 mg (100s and UD 100s}

ANDA -80 mg, 120 mg, 160 mg, 240 mg (100s and 1000s)
-120 mg & 240 mg (UD 100s)

4. Storage/dispensing recommendations:

RLD PI and carton - Store at CRT, between 15° to 30°C (59° to 86°F) container - Store at CRT, between 15°-30°C (59°-86°F)
Container - Dispense in a well-closed container (USP).

ANDA PI, container, and carton - Store at CRT , 15° to 30°C (59° to 86°F) container - Dispense in a tight, light-resistant container.

5. Bio. is pending.

6. The following information pertains to the 120 mg tablet only, which was added as a new strength with the 10-14-98 submission:

a. Closure:

100s - CRC [non CRC, not for marketing, for stability purposes]
1000s - non CRC
unitdose- foil aluminum push through
[Vol. B3.2, p. 000546]

b. The physical description and imprints of the 120 mg tablet in the HOW SUPPLIED section is consistent with the firm□s finished dosage statement.
[Vol. B3.2, p. 000782]

c. Inactive ingredients:

See NOTE TO THE CHEMIST

7. The following is from the previous review/reviewer:

a. This is a first generic.

b. The firm has accurately described the appearance of the tablets (pp 3345, 3356, 3367 vol B 1.4).

c. The inactives are accurately listed in the DESCRIPTION section (p 2333 vol B 1.2).

d. GenPharm Inc is the sole manufacturer (p 2410 vol. B 1.2).

Date of Review: 9-10-99 Date of Submission: 9-9-99

Primary Reviewer: Adolph Vezza Date: 9/15/99

A. Vezza

Team Leader: Charlie Hoppes Date: 9/15/99

Concur 9/15/1999

Telecon

Date: July 1, 1999

ANDA #: 75-237

Firm: Genpharm Inc.

Drug: Sotalol tablets, 80, 160, 240 mg

Participants: Ubrani V. Venkataram, Ph.D. and M. Kandasamy (tel: 416-207-1216, Ext. 223)

U.V. Venkataram 7/12/99.

Summary:

Firm had called to request for clarification regarding our comment on blend uniformity sampling. The firm said that the process will be validated for the first three production batches and the blend uniformity analysis (BUA) will be discontinued. I explained to them that, since the product includes less than of the active, we would require them to conduct BUA test on all post-approval batches. The firm asked whether they can discontinue the test after gathering sufficient data. I told them that we would not allow deletion of this test but it would be the responsibility of the field to monitor this. They wanted to know what would be an appropriate sampling plan for the production batches and whether they could sample the drums instead of the blender. I agreed that they could sample the drums. After some discussion it was agreed that the firm should at least take 2 samples from each drum and a minimum of 6 samples. The firm said they would amend the application accordingly.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-237** Date of Submission: **October 31, 1997**

Applicant's Name: **GENPHARM INC.**

Established Name: **Sotalol HCl Tablets, 80 mg, 160 mg, 240 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Please note that the established name for this drug product is "Sotalol Hydrochloride Tablets" ("Sotalol HCl Tablets" may also be used). Please revise your labels and labeling accordingly.

   b. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

   c. We encourage you to differentiate your product strengths by boxing, contrasting colors, or some other means.

2. CONTAINER 100s and 1000s (80 mg, 160 mg, 240 mg)

   a. See GENERAL COMMENTS above.

   b. You may delete "Sotalol Hydrochloride" following the strength.

   c. "**USUAL DOSAGE**" should be in bold print.

3. UNIT DOSE BLISTER

   See GENERAL COMMENTS (a) above.

4. UNIT DOSE CARTON

a. See GENERAL COMMENTS (a) and (b) above.

b. (59° to 86°F) - "to" rather than "TO".

5. INSERT

a. GENERAL COMMENTS

i. See GENERAL COMMENTS (1)(a) above.

ii. Replace the hyphen with the word "to" throughout the text of the insert where it occurs expressing a range of numbers or dosage, or a time period.

b. DESCRIPTION

i. First sentence - Sotalol hydrochloride is ...

ii. Delete the second sentence (It is supplied ...). This information is presented in the HOW SUPPLIED section.

iii. Replace the black square in front of "HCl" in the structural formula with a black dot.

iv. Revise the last paragraph as follows:

Sotalol Hydrochloride Tablets contain either 80 mg, 160 mg, or 240 mg of sotalol hydrochloride. In addition they also contain the following ... and stearic acid. (Note the change in text and the period after "acid").

c. CLINICAL PHARMACOLOGY

Delete "hydrochloride" throughout this section wherever it occurs except in the following places:

i. Mechanism of Action - second sentence

ii. Hemodynamics - first sentence

iii. Clinical Actions

A). Second occurrence in the paragraph beginning "In a double-blind..."

B). First occurrence in the paragraph beginning "In a large double-blind ...

iv. Pharmacokinetics - Second occurrence

d. INDICATIONS AND USAGE

i. First sentence - Sotalol Hydrochloride Tablets are indicated ...

ii. Delete all other occurrences of "hydrochloride" throughout this section.

e. CONTRAINDICATIONS

Revise to read as follows:

Sotalol Hydrochloride is contraindicated in ... to sotalol.

f. WARNINGS

Delete "hydrochloride" throughout this section except in the following places:

i. Second occurrence in the paragraph beginning "The applicability of ..."

ii. Abrupt withdrawal - the second occurrence

g. PRECAUTIONS

i. Please be consistent on subsection and sub subsection headings throughout this section (e.g., "RENAL IMPAIRMENT" and "DRUG INTERACTIONS" are subsections of "**PRECAUTIONS**" and should appear with less prominence).

ii. Delete "hydrochloride" throughout this section.

iii. Pregnancy Category B - Revise this heading to read:

Pregnancy: *Teratogenic Effects*: Pregnancy Category B:

iv. Pediatric Use

A). Delete "hydrochloride".

B). "pediatric patients" rather than "children".

h. ADVERSE REACTIONS

i. Delete "hydrochloride" throughout this section.

ii. Table - Indent the second line of a "**Body as a whole**" entry as shown below:

peripheral vascular
disorder

upper respiratory tract
problem

iii. Potential Adverse Effects - "pruritus" (spelling).

i. OVERDOSAGE

Delete the third occurrence of "hydrochloride".

j. DOSAGE AND ADMINISTRATION

i. Delete "hydrochloride" in the second sentence and in the sentence immediately before the "**Dosage in Renal Impairment**" subsection and all others which occur from this subsection through to the "HOW SUPPLIED" section.

ii. Dosage and Renal Impairment

A). Decrease the prominence of the heading.

B). Replace the hyphens with the word "to" in the table.

C). Delete the last paragraph of this subsection and replace it with the following text:

... table above).

Pharmacokinetic findings in patients requiring chronic hemodialysis is limited to six patients in two studies. In these patients, terminal elimination half life is prolonged to 40 hours in the interdialysis period and approaches 7 hours during dialysis. It is estimated that 20% to 40% of sotalol is removed during dialysis and that a slight rebound of plasma concentration is

noted post dialysis. Extreme caution must be taken in renal failure requiring hemodialysis, usual parameters of safety and efficacy (heart rate, QT interval and control of arrhythmia) must be closely monitored.

k. HOW SUPPLIED

i. Sotalol Hydrochloride Tablets are available ...

ii. See GENERAL COMMENTS (1)(a) and (1)(b) above.

iii. Include the dispensing statement as seen on your container labels:

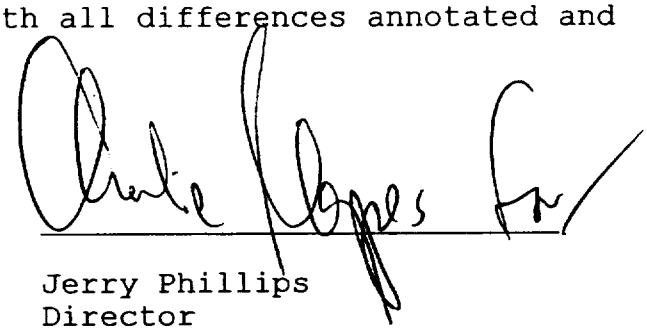
Dispense in a tight, light-resistant container.

iv. Please indicate that tablets are embossed.

Please revise your labels and labeling, as instructed above, and submit final printed container and unit dose labels, and final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Telecon

Date: 111997

Time: 0945

ANDA #: 75-237

Firm: Genpharm Inc.

Drug: Sotalol tablets, 80, 160, 240 mg

Participants: Gregg Davis, FDA and Bruce Goddard, Lipha

Agenda:

I called Bruce in need of some explanation and revision. I asked him for DMF authorization form the DMF holder not from the supplier of the active drug substance. The other alternative would be to supply a letter from Profarmaco authorizing Gyma to grant authority to FDA for accessing Profarmaco's DMF. My other concern was that the lot number mentioned in the Bio executive summary was different from the lot number used in the dissolution tests and the stability. He said he would check it out.